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REMARKS

Claims 1-28 are now pending. The Applicants respectfully request the Examiner to carefully reconsider the rejections in view of the amendments to the claims presented herewith and the following remarks.

Objection

Claim 12 stands rejected as allegedly failing to limit the scope of the claim from which it depends.

The Applicants respectfully highlight to the Examiner that claim 12 in fact limits the scope of claim 2 in that Claim 12 requires 3 or more layers whereas claim 2 is more broad in that it requires 2 or more layers. Claim 12, for example, does not encompass 2 layers (the subject matter is limited to 3 or more) - yet claim 2 (more breadth (2 or more)) encompasses 3 layers, for example.

The Applicants respectfully request the Examiner to withdraw the objection.

35 USC §112.1 Written Description

The Applicants respectfully request the Examiner to withdraw the rejections in view of the amendments to claims 13 and 26 presented herewith.

35 USC §112.2

The Applicants thank the Examiner for pointing out antecedent basis issues with reference to claims 9, 17, and 26. The Applicants respectfully request the Examiner to withdraw the rejections in view of the amendments presented herewith.

Claims 18-20

Claim 18 is amended herewith to properly depend from claim 17. The Applicants respectfully request the Examiner to withdraw the rejection.

Claims 19-21

Claims 19-21 are amended herewith to recite that the drug is released, *per se*, to address the issue raised. The Applicants respectfully request the Examiner to withdraw the rejection.

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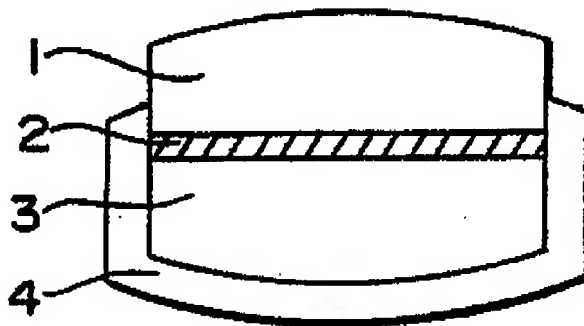
35 USC §§102 and 103 - Conte U.S. 4,865,849 in view of cited disclosures

A. Chronotherapy tablets of the present invention are provided which comprise a coating which envelops the core and at least one exposed release face substantially perpendicular to the longitudinal axis of the core, i.e., flat and circular and flush with the coat, in sharp contrast to the disclosure of Conte.

As the core is covered on all sides and only the circular release face is exposed, the release of drug occurs from this face. When the core imbibes gastrointestinal fluids, the top layer dissolves and a new layer of equal surface area is exposed, thereby keeping the surface area of the dissolving front constant throughout the dissolution process. As the rate of drug release is proportional to the dissolving surface area, the rate of drug release remains constant. It is well known to minimize the toxicity and yet, to remain in effective therapeutic range, a drug must be given at a constant rate. When the core dissolves rapidly and the drug is released instantly as in the case of Conte's design of the top layer, the concentration of the drug in blood rises past the therapeutic level to toxic level and thus raising the possibility of toxic effects.

Conte describes, suggests and contemplates a tablet that exhibits a protruding core and a barrier layer. Particularly, at Col.1, line 24, Conte specifies:

The active substance release mechanism is the following: on contact with water or aqueous liquid, the uncovered part 1 of the tablet rapidly disintegrates; this therefore results in release of the first medicament portion, leaving as residue the casing 4 closed by the barrier layer 2 and containing the second medicament portion in 3.



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The therapeutic entity of the present invention is capable of providing several pulses of drug delivery; three pulses, for example, of the same drug, different drugs, or the same or different combinations, in 24 hours. Pulses may be delayed as described herein; however, between pulses one or more drugs for example, can be released at a constant rate. Therapeutic entities described herein are structurally configured to effect various combinations of pulse release, constant release, and delayed release of compounds upon oral administration.

B. A further distinction from the disclosure of Conte is that embodiments of the present invention (see, amendment to claim 2) comprise a coating which envelops the core comprising water-soluble pore-forming material(s) that substantially leach out of the coat and thereby introduce mechanical instability and allow the coat to disintegrate after release of the active compound is complete. The pores, however, do not substantially affect the release rate of the active ingredient.¹ The coat remains intact throughout the delivery period but disintegrates prior to evacuation from the colon.

C. The Applicants further respectfully amend claim 5, for example, herewith to emphasize a further distinguishing feature of certain chronotherapy tablet embodiments of the present invention. Claim 5 to the present invention is amended herewith to be limited to two release-face embodiments, i.e., two release faces, one release face at a first end of the core and one release face at a second end of the core.² The claim 5 embodiment of the current invention comprise exposed layers at each end of the core as primary release faces.

Since none of the claims now pending encompass anything within the disclosure of Conte the subject matter cannot be anticipated as a matter of law. The Applicants respectfully request the Examiner to withdraw all rejections under 35 USC § 102.

Since none of the claims now pending encompass anything contemplated or suggested by the disclosure of Conte in combination with any of the cited references the subject matter cannot

¹ The Examiner is respectfully referred to paragraph 61, for example, of the specification as filed.

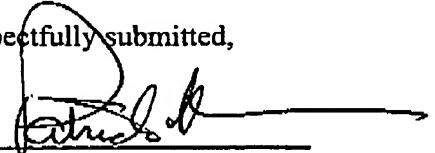
² The Examiner is respectfully referred to paragraphs 24-25, for example, of the specification as filed.

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be obvious as a matter of law.³ The Applicants respectfully request the Examiner to withdraw all rejections under 35 USC § 103.

The Applicants respectfully submit that claims 1-28 are in condition for allowance. Early action toward this end is courteously solicited. The Examiner is kindly encouraged to telephone the undersigned in order to expedite any detail of the prosecution. The Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 02-4800.

Respectfully submitted,



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³ It is axiomatic that a claimed invention is not obvious solely because it is composed of elements that are all individually found in the prior art. The factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000).